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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/234,532	01/21/1999	ALFRED SAPSE	1398-002	5965

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JOSEPH A. MAHONEY
MAYER, BROWN, ROWE & MAW
P.O. BOX 2828
CHICAGO, IL 60690-2828

EXAMINER	
OWENS JR, HOWARD V	
ART UNIT	**PAPER NUMBER**
1623	

DATE MAILED: 11/18/2003

35

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/234,532	Applicant(s) SAPSE, ALFRED	
	Examiner Howard V Owens	Art Unit 1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1- 3, 5, 10, 11, 13, 14 and 21-36* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1- 3, 5, 10, 11, 13, 14 and 21-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a)☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *33*.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Detailed Action

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/16/02 has been entered.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 USC § 103

Claims 1- 3, 5, 10, 11, 13, 14 and 21-36 are rejected under 35 U.S.C. § 103 as being unpatentable over Sapse, *Psychoneuroendocrinology*, Vol. 22, pp. S3 - S10 (1997) in combination with Devita et al., AIDS,4th edition, pp. 501-504, Lemay et al., Int. Conf. AIDS, vol.5 (1989) and Burnet et al., *Medical Hypotheses*, vol. 13, pp. 313-44 (1984).

Claims 1 and 2 are drawn to a composition comprising at least one anti-HIV drug and cortisol blocker comprising procaine HCl, zinc heptahydrate and ascorbic acid.

Claim 3 is drawn to a composition comprising at least two anti-HIV drugs and a cortisol blocker.

Claims 5, 10, 11, 13 and 14 are drawn to a method for the management of side effects associated with the administration of anti-HIV drug therapy comprising administration to a patient a therapeutically effective amount of at least one cortisol blocker.

Claims 21-36 are drawn to various concentrations of the anti-HIV drug/cortisol composition.

Sapse teaches that patients with AIDS have demonstrated higher than normal cortisol levels and that these increased cortisol levels cause deleterious effects; moreover that cortisol blockers such as procaine HCl, DHEA, ketoconazole have been used in HIV therapy to combat these deleterious effects (p. S5 – S8). Lemay et al. supports these teachings as it teaches the cortisol blocker ketaconazole in combination with the anti-

HIV drug Zidovudine (AZT). Burnet et al. additionally teaches that procaine and vitamin C are both cortisol blockers useful in conditions where there are elevated cortisol levels, pp. 37-38. Neither Sapse, Burnet nor Lemay teach combining two HIV drugs with a cortisol blocker.

Devita bridges the nexus for the use of two or more HIV drugs with a cortisol blocker as Devita et al. teach that combinations of anti-HIV drugs are beneficial in treating HIV infection for several reasons: Two or more drugs may have additive or synergistic interactions that produce better efficacy than with either drug alone, lower doses than those employed in monotherapies- possibly decreasing toxicity, delaying the emergence of a resistant virus that can escape drug inhibition, and targeting of different cellular and tissue reservoirs of the virus; particularly AZT in combination with ddC, ddI or 3TC as the combination of AZT with these agents present stronger synergy over monotherapies or treatment of AZT resistant isolates (DeVita et al., AIDS, 4th edition, pp. 502-504).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining the differences between the prior art and the claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.
> 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

A *prima facie* case of obviousness is supported when the prior art alone would have appeared to suggest doing, at the time the invention was made, what the applicant has done. It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made that a cortisol blocker could be used in a composition with an anti-HIV drug. One of skill in the art would have been provided with a clear motivation and a reasonable expectation of success to combine the teachings of Sapse with that of Lemay and Devita given that any method of treatment would seek to reduce the catabolic effects associated therein, as Lemay and Devita teach the benefits of combination therapies wherein cortisol blockers are used in the treatment of HIV to

increase the synergistic effects of an anti-HIV drug and cortisol blockers are shown by Beale to reduce the catabolic effects of the disease itself, whether the catabolic effects are associated with the use of the anti-HIV drug or the disease itself, one of skill would include cortisol blockers in the treatment regime to reduce or alleviate these catabolic effects as an adjunct to a combination therapy.

The prior art need not explicitly state each side effect, only provide a motivation to combine the two compounds, in this case, applicant's side effects would be viewed as catabolic effects, and given that Lemay and Devita teach the benefits of combination therapies wherein cortisol blockers are used in the treatment of HIV to increase the synergistic effects of an anti-HIV drug and cortisol blockers are shown by Sapse to reduce the catabolic effects of the disease itself, whether the catabolic effects are associated with the use of the anti-HIV drug or the disease itself, one of skill would include cortisol blockers in the treatment regime to reduce or alleviate these catabolic effects as an adjunct to a combination therapy.

Response to Arguments and Declaration

Applicant argues that none of the references, alone or in combination, teach the combination composition as recited in claim 1, a composition comprising at least one anti-HIV drug and cortisol blocker comprising procaine HCl, zinc heptahydrate and ascorbic acid. The examiner has provided the additional reference of Sapse to support the motivation to use cortisol blockers with HIV therapy; moreover, the Sapse reference clearly counters applicant's assertions regarding the use of ketaconazole with an HIV drug, wherein applicant primarily asserts that one of skill in the art would not have been motivated to use ketaconazole in HIV therapy. Assuming arguendo that the Lemay reference is disregarded, Sapse clearly teaches that "ketaconazole is now increasingly used in AIDS, with or without the presence of fungal infection." (p. S7).

Applicant's additional data in support of the declaration of 9/18/2000 has been considered but is not found persuasive. The declaration under 37 CFR 1.132 filed 9/18/2000 is insufficient to overcome the rejection of claims 1- 3, 5, 10, 11, 13, 14 and 21-36 based upon 35 U.S.C. § 103 as being unpatentable over Sapse,

Psychoneuroendocrinology, Vol. 22, pp. S3 - S10 (1997) in combination with Devita et al., AIDS,4th edition, pp. 501-504, Lemay et al., Int. Conf. AIDS, vol.5 (1989) and Burnet et al., *Medical Hypotheses*, vol. 13, pp. 313-44 (1984).

Applicant primarily asserts that the addendum to the declaration demonstrates that there is a synergistic affect when the cortisol blockers are combined over the administration of each separately.

It should be noted that claim1 is drawn to a composition containing at least one cortisol blocker and at least one HIV drug. Thus, not all of the claims are drawn to the use of more than one cortisol blocker, which is the basis of the declaration. For those claims drawn to the use of more than one cortisol blocker, the declaration seeks to overcome the art of record by a showing that there is a synergism obtained with the use of more than one cortisol blocker. Synergism is treated like any other property. The showing should demonstrate that synergism is unexpected. *In re Huellmantel*, 139 USPQ 496; *In re Meinhardt*, 157 USPQ 270. As cited supra, the prior art has set forth the expected result and motivation to combine an HIV drug and a cortisol blocker; moreover, it is inherent that the addition of a cortisol blocker promotes a synergistic effect when combined with an HIV drug since the cortisol blocker is countering the deleterious effects of HIV from the elevated cortisol levels which were not primarily combated nor targeted through the use of conventional HIV drugs.

Additionally, when viewing declarative evidence asserting an unexpected result, per MPEP 716.02:

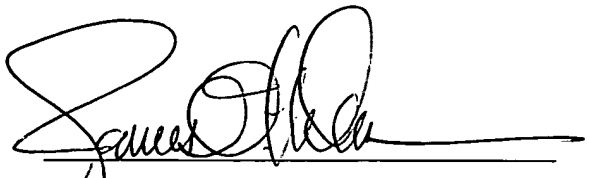
"Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). Merck & Co. Inc. v. Biocraft Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989). However, a greater than additive effect is not necessarily sufficient to overcome a prima facie case of obviousness because such an effect can either be expected or unexpected. Applicants must further show that the results were greater than those which would have been expected from the prior art to an unobvious extent, and that the results are of a significant, practical advantage. Ex parte The NutraSweet Co., 19 USPQ2d 1586 (Bd. Pat. App. & Inter. 1991) (Evidence showing greater than additive sweetness resulting from the claimed mixture of saccharin and L-aspartyl-L-phenylalanine was not sufficient to outweigh the

evidence of obviousness because the teachings of the prior art lead to a general expectation of greater than additive sweetening effects when using mixtures of synthetic sweeteners.)."

In the instant case, the unexpected result in relation to the scope of the claims and the prior art is whether there is an unexpected result that the use of more than one cortisol blocker with an HIV drug would have an unexpected result. The prior art has established that the lowering of cortisol in HIV patients with an anti-cortisol drug is not unexpected and is clearly beneficial in lowering the deleterious effects associated with higher than normal cortisol levels. The data presented in the May 2000 study shows that the level of inhibition of cortisol biosynthesis per cortisol blocker is relatively the same when the individual cortisol inhibitors are compared to the combination; moreover, assuming *arguendo* that there was a showing that the cortisol levels are lower when more than one cortisol blocker is used represents a difference in degree, not in kind, with respect to whether one of skill in the art would have expected the property of cortisol lowering to exist. Moreover, the May 2000 study actually demonstrates that the combination of more than one of the claimed cortisol blockers actually becomes ineffective with regards to cortisol lowering at a certain concentration (200 μM), when the same concentration is still effective through administration of individual cortisol blockers (emphasis added), which counters applicant's assertion of synergy.

In view of the foregoing, when all of the evidence is considered, the totality of the rebuttal evidence of nonobviousness fails to outweigh the evidence of obviousness.

Howard V. Owens
Patent Examiner
Art Unit 1623



James O. Wilson
Supervisory Patent Examiner
Technology Center 1600

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Howard Owens whose telephone number is (703) 306-4538 . The examiner can normally be reached on Mon.-Fri. from 8:30 a.m. to 5 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the Supervisory Patent Examiner signing this action, James O. Wilson can be reached on (703) 308-4624 . The fax phone number for this Group is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-1235.